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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,858	12/14/2001	Karen Koch	6225.200-US	7430

7590 10/22/2002

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EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/22/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,858	KOCH ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-32 and 34-53* is/are pending in the application.

4a) Of the above claim(s) *29-32 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election of the invention of Group II, claims 35-53 in Paper No. 9, received September 5, 2002, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 29-32 and 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected election, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9, received September 5, 2002.

Claims 29-32 and 34-53 are pending.

Claim Objection

Claim 53 is objected to because of the following informalities: the use of double colon in claim 53, line 1: "::", is considered improper. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for estradiol, does not reasonably provide enablement for other estradiol derivatives. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case, the specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that define "estradiol derivatives". It is not clear how one of skilled artisan would be able to select the appropriate compounds, which are structurally related to estradiol, to be employed in the instant method. There is not enough biological or physical chemical information provided by the instant specification in regard to the selection of the appropriate compounds. Therefore, Applicant fails to provide information and guidance allowing the skilled artisan to

ascertain these compounds without undue experimentation. In the instant case, only a limited number of "estradiol derivatives" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on all "estradiol derivatives", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term “derivative” in claims 35, 37-42, and 49 renders the claims indefinite. It is unclear what compounds are encompassed by the term “derivatives”.

The term "low" in claim 51 is a relative term which renders the claim indefinite. The term "low" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In the instant case, it is not clear what degree of systemic absorption of the estradiol compounds would be considered “low”.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 35-37, 43-48, 52-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Mettler and Olsen (Maturitus,1991;14:23-31 from the IDS received March 25, 2002).

Mettler and Olsen teaches a method of treating atrophic vaginitis by vaginally administering 25μg tablets of 17β-estradiol to post-menopausal women once-weekly or twice weekly for more than 3 months (See page 23, abstract; page 24 and 25, Subjects and Methods Section). Mettler and Olsen also teaches that the 17β-estradiol treatment is effective in relieving the symptoms of atrophic vaginitis such as vaginal dryness (See page 28, second paragraph, also Table 2). Please note that the lowering of the vaginal pH is considered as an inherent effect resulted from the exact same active method steps herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35, 38-42 are 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mettler and Olsen in view of Meignant (WO97/12600 from the IDS received March 25, 2002) and Vagifem monograph (Novo Nordisk, June 2000).

Mettler and Olsen teaches a method of treating atrophic vaginitis by vaginally administering 25μg tablets of 17β-estradiol (Vagifem®) to post-menopausal women once-weekly or twice weekly for more than 3 months (See page 23, abstract; page 24 and 25, Subjects and Methods Section). Mettler and Olsen also teaches that the 17β-estradiol treatment is effective in relieving the symptoms of atrophic vaginitis such as vaginal dryness (See page 28, second paragraph, also Table 2). Please note that the lowering of the vaginal pH is considered as an inherent effect resulted from the exact same active method steps herein.

Mettler and Olsen does not expressly teach the dosage of estradiol as between 1.5 to 4 μg daily, 2 to 3 μg daily, 5 to 15 μg twice weekly, 7 to about 13 μg twice weekly, or 9 to 11μg twice weekly. Mettler and Olsen does not expressly teach the estradiol tablet containing 53.7mg hypromellose, about 17.9mg lactose monohydrate, about 8 mg maize starch, and about 0.4 mg magnesium stearate. Mettler and Olsen does not expressly teach the tablet is coated with a film consisting of about 0.5mg hypromellose and about 0.06 mg Macrogel 6000.

Meignant teaches that low dose 17β-estradiol, which is less than 10μg, is useful in treating vaginal dryness and at the same time, the low dosage can minimize the systemic absorption of estradiol (See abstract).

Vagifem monograph teaches that the inert excipient of Vagifem tablet containing hydroxypropyl methylcellulose (hypromellose), lactose monohydrate, maize starch, and magnesium stearate (page 1, col. 1). Vagifem monograph also teaches that the film coating of the tablet containing hydroxypropyl methylcellulose (hypromellose) and polyethylene glycol (Macrogel 6000).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to employ the herein claimed dosage and regimen in the method of treating atrophic vaginitis of Mettler and Olsen. It would have been obvious for one of ordinary skill in the art at the time the invention was made to employ the herein claimed amount of the inert excipients into the tablet.

One of ordinary skill in the art would have been motivated to employ the herein claimed dosage and regimen in the method of treating atrophic vaginitis of Mettler and Olsen. Possessing the teaching of Mettler and Olsen and Meignant, one of ordinary skill in the art would optimize the result therapeutic parameters (e.g., dosage range, dosing regimens) to minimize systemic absorption of estradiol and systemic side effects thereby. One of ordinary skill in the art would have been motivated to employ the herein claimed amount of the inert excipients into the tablet because the optimization of amount of inert excipients would be considered as being within the purview of skilled artisan.

McCane ("Pathophysilogy: the biologic basis for disease in adults and children", published by Mosby, 1990, page 989) is cited to show the state of the art in regard to the relationship between vaginal pH and estrogen levels. Acidic vaginal pH is correlated to relatively high estrogen level and neutral or alkaline pH is correlated to low estrogen level (menopause).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
October 18, 2002

SREENI PADMANABHAN
PRIMARY EXAMINER 10/21/02